

**PREVENTING DEPRESSION IN LATER LIFE: A MODEL FOR LOW AND
MIDDLE INCOME COUNTRIES**

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Introduction to Revised Application

We thank the reviewers for extensive guidance based upon our initial application. We summarize our responses here: (1) How is the proposed study innovative and distinct from the original MANAS trial? We propose to extend the unanticipated prevention results of MANAS into a specific hypothesis-driven study. MANAS showed a relative risk difference at 6 months of 50% in the incidence of ICD-10 confirmed depression and anxiety disorders, in a mixed-aged sample of those receiving collaborative stepped care (12.7%) versus those receiving enhanced usual care (25.0%). We hypothesize that the MANAS intervention, modified to add other evidence-based components, and delivered by Lay Health Counselors, is not just a treatment intervention, but a preventive intervention, too. The specific focus on older adults in a LAMI country reflects both their growing numbers in LAMI countries and high exposure to risk factors for late life depression. This will be the first trial aimed at the prevention of depression in older people living in a LAMI country, using Lay Health Counselors and exploring a combination of approaches. We expect that it is possible to identify high-risk groups in which the incidence rates are higher than the 25% reported in MANAS, by better screening methods; and that the effects of the interventions can be further enhanced if a specific intervention for older adults is developed. An R34 is needed to examine these possibilities before going to a full-scale confirmatory trial.

(2) What is the theoretical rationale for the intervention? Brief, learning-based approaches which can be delivered by Lay Health Counselors are promising to address the mandate of the NIMH Strategic Plan (2.3) "to develop and test innovative interventions to reduce risk and positively alter trajectories of illness." These include approaches such as Problem Solving Therapy for Primary Care (PST-PC) and Brief Behavioral Treatment for Insomnia (BBTI). The rationale for selecting these approaches is both to enhance protective factors (such as coping skills) and to reduce vulnerability factors (such as insomnia). Teaching strategies for better sleep may diminish affective reactivity and enhance cognitive flexibility (thus capitalizing on a potential synergy with PST-PC). Since learning-based interventions are effective for treating prevalent cases of depression and insomnia, we ask whether they will also be acceptable, feasible, safe, and effective in preventing depression and anxiety disorders in at-risk elders in underserved LAMIs.

One major development since the original submission is that our colleagues at the London School of Hygiene and Tropical Medicine (LSHTM) and at Sangath (Goa) have been awarded one of the three NIMH Hubs for international mental health research (PI: Patel). The Hub (SHARE) offers a platform for the R34 and provides complementary expertise to the NIMH funded ACISR in late-life depression prevention and treatment at Pittsburgh (PI: Reynolds).

(3) Further specify the logic of key choices. We apologize for not specifying our approaches and logic model for the following issues: (a) expected effect size based on Goa/MANAS and Amsterdam/primary care trials (expected reduction in relative incidence of depression and anxiety: 25%-50%); (b) criteria for determining that a more intensive intervention would be used in a stepped care algorithm (criterion: persistence of subthreshold symptoms despite initial interventions); (c) eligibility criteria, i.e., low end cutoff for GHQ (to define eligibility, scores of 1-7 on the GHQ are proposed in the absence of a CISR-defined episode of major depression or anxiety disorder); (d) rationale for requiring no antidepressant use (because such subjects could have a partially treated episode of major depression or anxiety disorders); (e) description of primary care population served by two primary care clinics (data on age, gender, ethnicity, education, marital status and mental health status are now provided); (f) recruitment and description of team member roles and training in phase 1 (a multidisciplinary team, per the infrastructure provided by the new Hub, is now described); (g) analysis of qualitative data (under the leadership of Drs. Alex Cohen [LSHTM] and Neerja Chowdhary [Sangath]) is now specified, with published examples of the team's previous experience; (h) description of care as usual (content and process measures are now specified); (i) justification for dual focus on subthreshold symptoms of depression and on persons with major life stressors ("indicated" and "selective" prevention, respectively) is now provided; (j) systematic assessment of intervention delivery and fidelity (will be performed through use of audio tapes of randomly selected sessions and blind rating of fidelity); (k) strategies for engagement of persons in preventive interventions (through psychoeducation and tailoring interventions to subject preferences) are now given; (l) timeline of study activities (approximately 12 months for phase 1 formative work; and 24 months for pilot randomized depression prevention trial); (m) protection of human subjects re: confidentiality and stigma issues; (n) composition of Data Safety Monitoring Board (to ensure expertise in biostatistics, clinical trial design, ethics, and medical sociology); (o) relocation of randomization procedure from Pittsburgh to Goa; (p) description of resources available at Pittsburgh and Goa; and (q) resource allocation (63% to Goa, 33% to LSHTM, and 4% to Pittsburgh). Amended text is indicated with a vertical line in the left margin throughout.

SPECIFIC AIMS

Prevention of depressive and anxiety disorders is of great public health significance in Low and Middle Income Countries (LMICs), and represents one of the Grand Challenges in Global Mental Health (grandchallengesinglobalMH@NIH.org). Late-life depression and anxiety are of particular concern in LMICs due to rapid demographic transition and aging in countries such as India; increased prevalence of social conditions that are recognized as risk factors (e.g., living alone or living with a chronic disabling condition); and the weak response of health systems to address the needs (let alone the mental health needs) of the elderly. Because of the lack of mental health specialists there is a need to focus on prevention interventions that can be delivered by non-specialist and lay health workers in non-health care or primary care settings. The work proposed in this revised R34 application could inform policy and practice in the US by clarifying appropriate roles for lay and non-specialist workers in depression and anxiety prevention for populations with few mental health resources.

Meta-analyses of more than 30 randomized trials conducted in the West suggest that the incidence of new depressive and anxiety disorders can be reduced by about 25% over 1-2 years compared to usual care^{2,3} through the use of learning based psychotherapies (such as IPT, CBT, and PST). A recent study, the MANAS trial ("project to promote mental-health" in the Konkani language) conducted in Goa, India^{1,4} demonstrated that the use of lay health counselors, as part of a collaborative stepped-care intervention, increased recovery rates from common mental disorders (anxiety and depression) in a mixed-age sample of patients of public primary care facilities. An unanticipated finding was that the MANAS intervention also reduced the incidence of common mental disorders in those with initially sub-threshold (subsyndromal) depressive and anxiety symptoms. Given the shortage of mental health specialists in LMICs, MANAS addressed the important strategy of task shifting, that is, the rational redistribution of tasks among health workforce teams in order to make more efficient use of lay human resources. We propose that the time is right to investigate the use of non-specialists in the effort to prevent late-life depression and anxiety in LMICs. We think that the effects of the MANAS intervention can be further enhanced if a specific intervention for older adults is developed.

Specific Aim (1) formative research (months 1 – 12): following Medical Research Council Guidelines for the development of complex interventions⁵, we will create and standardize a MANAS-derived depression and anxiety prevention intervention ("MANAS/Depression Prevention") for use by lay health counselors (LHCs) in primary care clinics in Goa. We will develop an intervention manual based on the original MANAS trial and best practices for depression and anxiety prevention from the global literature. Via systematic study of an uncontrolled case series (enrolling 20 subjects), we will test the feasibility and acceptability of MANAS/DP. We anticipate that MANAS/DP will comprise psychoeducational interventions delivered by LHCs and previously shown to have prevention efficacy: (a) education about symptoms of depression and anxiety, (b) instruction in breathing exercises and relaxation to manage symptoms of anxiety, (c) scheduling of activities to manage symptoms of depression, and (d) provision of social casework as needed. In addition, based upon a review of global depression prevention literature, we will explore the feasibility and acceptability of two approaches that appear to work by strengthening protective factors: Problem Solving Therapy for Primary Care (PST-PC) and Brief Behavioral Treatment for Insomnia (BBTI). The products of Specific Aim (1) will be a prevention manual to standardize the implementation of MANAS/DP for further testing in a pilot randomized prevention trial (Specific Aim 2), together with recruitment and assessment protocols and a randomization procedure.

Specific Aim (2) pilot randomized prevention trial (months 13 – 36): Via the use of a pilot randomized prevention trial (MANAS/DP) we will: gather data on the feasibility of identifying, enrolling, randomizing and retaining participants; implement the experimental intervention and enhanced usual care; identify "real world", barriers and develop strategies for addressing them; and assess the fidelity of the MANAS/DP implementation. As recommended in the R34 program announcement (PAR-09-173), we will collect measures of feasibility, acceptability, tolerability, and safety, rather than conducting formal tests of outcome or attempting to obtain an estimate of an effect size (because estimates are likely to be inflated and unstable.) These data will be critical to a subsequent confirmatory randomized depression prevention trial based in Goa and to our long-term goal of scalable depression prevention in LAMIs.

RESEARCH STRATEGY: SIGNIFICANCE AND INNOVATION

In this section we describe the public health significance and innovation of collaborative-care depression prevention delivered by LHCs, the limitation of existing treatment interventions, and why a preventative intervention is needed. In addition we provide a conceptual link between depression and MANAS/DP, including possible mechanisms of action.

Why is prevention of major depression in later life important, especially in low and middle income countries?:

The investigators have recently established an international consortium for depression prevention researchers (www.preventionofdepression.org)¹ and have reviewed the public health need for depression prevention research in older adults in Low and Middle Income Countries (LMICs).² We noted: (1) The number of older adults in LMICs, including India, will grow substantially in the next few decades. According to the US Census National Database (<http://www.census.gov/ipc/www/idb/informationgateway.php>), the 60+ population in India was about 99.4 million persons (9%). The projections for 2030 are 192.7 million (14.3%). (2) Major depressive episodes in older adults are prevalent and disabling (6-10% in primary care settings; 30% in inpatient medical and long term care settings). The point prevalence of depression among elderly persons in a rural South Indian community was estimated at 12.7% (95% CI 10.6-14.8).³ (3) The disorder often runs a relapsing or chronic course, and social factors, particularly related to economic or social disadvantages (low education and violence), are major determinants.⁴⁻⁶ (4) The condition is often co-morbid with other chronic conditions like diabetes, amplifying the disability associated with these conditions and worsening family caregiver burden.⁷⁻⁹ Depression is associated with worse physical health, e.g., cardiovascular or HIV outcomes, through poorer treatment adherence.⁷ (5) Depression is associated with excess mortality after myocardial infarction, stroke, and cancer and is the major risk factor for suicide in old age.¹⁰ (6) Available treatments are only partially satisfactory in reducing symptom burden, sustaining remission, and averting years lived with disability.^{11;12} (7) The treatment gap for people with mental disorders has been extensively documented, especially in LMICs where up to 90% of people with mental disorders do not receive cost-effective treatments.¹³ (8) The great scarcity of mental health specialists in most countries and the inequity of the distribution of these specialists is a major barrier to closing the treatment gap. The existence of the treatment gap and the attendant workforce issues underscore the need for developing effective models of prevention that can be implemented by health workers with shorter training and fewer qualifications, in order to make more efficient use of the available human resources for health.^{14;15} Finally, (9) preventing depression in older adults may be cost-effective.^{16;17}

In summary, the development of depression prevention strategies effective in LMICs would be a means of addressing multiple inequalities (e.g., treatment gaps, workforce barriers) in global mental health. In India, based upon the projections above for the year 2030, we project the number of older adults with depression to be 192.7 million x 0.127=24.5 million. A reduction of 50% in incidence could potentially affect over 12 million individuals if effective prevention strategies were widely employed. Even a 25% reduction would have significant impact on a large population. In a recent study, Barnes and Yaffe estimated that prevalent cases of Alzheimer's disease attributable to depression range from 506,000 to 1,078,000 subjects in the U.S. Accordingly, the prevention of 10% and 25% of lifetime cases of depression may reduce the prevalence of Alzheimer's disease by 68,000 and 173,000, respectively. Therefore mental health policies targeting the prevention, early detection, and treatment of depression across the lifespan (particularly later in life) could also contribute to a reduction in the incidence and prevalence of dementia.¹⁸

What Are Promising Approaches Circa 2012?

Both randomized prevention trials and epidemiological modeling suggest that prevention of major depression in later life may be most efficiently accomplished by targeting elderly persons who experience risk factors particularly functional limitations as a result of illnesses such as stroke or macular degeneration, have a small social network, and/or have subthreshold (i.e., subsyndromal) symptoms.^{16;19;20} "Efficiency" of interventions to prevent depression encompasses both the impact of the intervention and the effort required to implement it. Impact is reflected in the proportion of cases that would be prevented if the adverse effects of the targeted risk factor were completely blocked (attributable fraction). Effort is reflected by the number of persons who would need to receive a depression prevention intervention to avoid one new case of late life depression ("number needed to treat", or NNT). Schoevers et al.⁹ have estimated that preventive interventions would have the highest impact and lowest effort in the presence of subthreshold depressive symptoms (NNT = 3-4 in

"indicated" prevention, versus NNT's of 7-9 in "selective" prevention). That is, preventive interventions may have more impact in older adults who already have subthreshold symptoms ("indicated prevention") than in persons without such symptoms even though those with subthreshold symptoms typically also have other risk factors such as disabilities from medical illness ("selective" prevention). In our current depression prevention studies, and in the work proposed here, we will track both subthreshold symptoms and psychosocial stressors because patients with subthreshold symptoms frequently endorse multiple stressors.⁴⁰ We see our proposal as focusing primarily on "indicated" prevention, enrolling patients with subsyndromal symptoms.

A recent report from Amsterdam²¹ evaluated indicated prevention in Dutch primary care patients above the age of 75. With the objective of determining the efficacy of an indicated stepped-care prevention program, 170 individuals with sub-threshold symptom levels of depression or anxiety were followed. Comprising the intervention program were four sequential steps, each of three months duration: watchful waiting, cognitive behavioral therapy-based bibliotherapy, problem solving therapy, and referrals to primary care if the patient needed antidepressant medication. The incidence of major depressive episodes and anxiety disorders was reduced by half over a one-year follow-up period. Thus, about 24% of patients randomly assigned to treatment as usual experienced the onset of major depressive episodes or of anxiety disorders, compared with 11% of participants receiving the stepped-care for depression prevention (NNT = 4). This stepped-care algorithm was also demonstrated to be cost-effective.¹⁷

A study exemplifying selective prevention enrolled patients with recent stroke (n=176).¹⁹ In the study, non-depressed patients receiving placebo (n=58) were significantly more likely over the course of 12 months to suffer a major or minor depressive episode than those patients (n=59) administered either an SSRI (selective serotonin re-uptake inhibitor) alone (low-dose escitalopram, 5mg/day), or receiving a course of problem-solving therapy (n=58).¹⁹ This study found an NNT of approximately 8.

Promising interventions and rationale for their use: Brief learning-based approaches, already shown to have efficacy in the treatment of depressive disorders, pain, or insomnia disorders, offer a promising strategy to address the mandate of the NIMH Strategic Plan (2.3) "to develop and test innovative interventions to reduce risk and positively alter trajectories of illness."(<http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml#strategic-objective2>) While antidepressant medications are the most widely used modality for treating prevalent cases of major depression, their use in subthreshold depression may be ill-advised due to a lack of evidence for efficacy in mild depression, as well as adverse effects in older adults such as hyponatremia, risk for falls, bone demineralization, and cataracts.²² Psychological interventions may be desirable for reasons of safety and patient preference. Problem solving therapy (PST), in which behavioral activation is an important component, has been used in depression prevention studies successfully,^{19-21;23} is more easily utilized than Interpersonal Psychotherapy or Cognitive Behavioral Therapy, and can be embedded within a clear service model.¹¹ Teaching coping skills may enhance resilience to stress, diminishing the sense of loss of control (feeling trapped or helpless) at the core of depression. Similarly, teaching strategies for better sleep (because poor sleep is a known and well-established risk factor for depression) may diminish affective reactivity and enhance cognitive flexibility on the part of both care recipients and caregivers.^{24;25} Thus, there may be a synergy between PST-based approaches and those that enhance sleep quality. In this context, Brief Behavioral Treatment of Insomnia (BBTI) seems particularly promising, since it has been shown to improve sleep quality and to reduce symptoms of depression and anxiety.²⁵ Moreover, learning-based, skills-enhancing interventions are effective for prevalent cases of depression and insomnia. Interventions such as PST and BBTI are also practicable: safe, cheap, deliverable by general medical clinicians (including nurses, social workers, and potentially lay health counselors), and more likely to be acceptable to older adults than the use of antidepressant medication before major depression is diagnosable.

Innovation/Impact:

This study will generate the first evidence of potentially scalable interventions for prevention of depression in later life from an LMIC in the midst of rapid demographic transition. The emphasis on depression prevention via use of LHCs and the exploration of a combination of approaches are both innovative. Our application proposes to take the unanticipated prevention results of MANAS toward a specific hypothesis-driven study. MANAS showed a risk difference at 6 months of 12.3% in the incidence of ICD-10 confirmed common mental disorders (especially mixed anxiety and depression) in a mixed-age sample (mean age in early 40s) in those

receiving collaborative stepped care utilizing LHCs (12.7%) versus those receiving enhanced usual care (25.0%). We expect it is possible to identify high-risk groups in which the incidence rates are higher than the 25% reported in MANAS, by better screening methods; and that the effects of the interventions can be further enhanced if a specific intervention for older adults is developed. Moreover, our specific focus on older adults in an LMIC (an imperative driven not only by the demographic transition but also older adults' high exposure to risk factors for depression, i.e., subthreshold symptoms, insomnia, illness-related disabilities, physical pain, and social isolation) is an innovative approach to reducing the global disease burden of depression. Finally, since learning-based interventions, such as problem-solving therapy for Primary Care (PST-PC) and Brief Behavioral Treatment for Insomnia (BBTI) are effective for treating prevalent cases of depression and insomnia, it is innovative and important to ask if these interventions will be acceptable, feasible, safe and effectively administered by LHCs to preventing depression in at-risk elders in low- and middle-income countries.

Research Strategy: Investigative Team and Preliminary Studies

The investigative team consists of scientists from the London School of Hygiene and Tropical Medicine (Patel and Cohen), the Department of Psychology at the Free University in Amsterdam (Cuijpers), the NIMH sponsored ACISR in Late-Life Depression Prevention at Pittsburgh (P30 MH090333: Reynolds, Dew, Albert, Anderson), and on-site investigators and staff in Goa, India (Dias, Chowdhary, Naik) previously involved in the conduct of both the MANAS/RX trial and in a task-shifting trial promoting mental health of care givers of older adults with dementia.²⁶ The investigators have conjointly authored a review, "Early Intervention to Reduce the Global Health and Economic Burden of Major Depression in Older Adults," recently published in the Annual Review of Public Health.²

Patel and colleagues in India (including Chowdhary) developed a community lay health counselor (LHC) led intervention which combined a psychological treatment (psychoeducation and interpersonal psychotherapy: IPT) and antidepressants in a collaborative, stepped-care delivery model. The intervention group comprised 1360 and the control group, 1436 participants. Based on intent-to-treat sample completion rates of 85-88%, the intervention had an impact on 6-month recovery rates from common mental disorders (65% vs. 52.9% [NNT = 8], with a stronger effect in public facility attendees: 65.9% vs 42.5%; [NNT = 4). In sub-threshold cases, there was evidence of a protective effect of the intervention overall in terms of 6-month prevalence rates of ICD-10 confirmed mental disorders: 12.3% in LHC-led collaborative stepped care versus 25.0% in enhanced usual care. In addition to MANAS, **Dias and Patel** also conducted the HomeCare Trial,²⁶ the first dementia caregiver support trial in an LMIC, which showed reduced caregiver depression.

Patel and colleagues have just been awarded one of three NIMH Hubs for international mental health research, which can be a platform for the R34 and which provides expertise complementary to Pitt's ACISR.

Cuijpers and colleagues in Amsterdam (Departments of Psychology and Psychiatry, Free University) investigated the impact of a stepped-care model of depression prevention in 170 Dutch primary care patients aged 75 and older with sub-threshold symptoms of depression or anxiety.¹⁷ The intervention reduced the incidence of anxiety disorders and major depressive episodes by 50% over one year, relative to care as usual (24% versus 12%)-- a result similar in magnitude to the unanticipated result of MANAS (25% v. 12.3%).

Reynolds, Dew, Albert, and Anderson (University of Pittsburgh Department of Psychiatry and Graduate School of Public Health) have conducted three long term NIH-sponsored maintenance trials using a variety of psychosocial (e.g., IPT) and pharmacologic interventions (TCA, SSRI, and choline esterase inhibitor) to prevent depression recurrence and to slow cognitive decline in older adults,^{5;6;27} in addition to a suicide prevention trial in older primary care adults.⁷ Currently, **Reynolds, Albert, and Dew** are conducting an NIH-sponsored (P60 MD000207; P30 MH090333) randomized controlled prevention trial of indicated prevention to evaluate the efficacy of problem solving therapy to prevent episodes of major depression, diminish disability, and improve health related quality of life in older low-income adults who have mild symptoms of depression.²⁸ Concurrently, we are also tracking participant's other risk factors for depression. Thirty-five percent of the sample (n = 246) are African American. Both subthreshold symptoms and psychosocial stressors are being tracked in study participants.

Cohen, Dew, and Reynolds reported that residents of low-income neighborhoods had lower overall rates of treatment response and greater persistence of suicidal ideation when compared to residents of higher-income neighborhoods.⁴ This observation indicates the importance of directing depression prevention efforts at socioeconomically disadvantaged persons who, once depressed, seem to benefit less from treatment.

Finally, Buysse, Reynolds et al. have demonstrated the efficacy of Brief Behavioral Treatment for Chronic Insomnia (BBTI) in older primary care adults (n = 79): as evidenced by both a higher response rates than an information control condition (67% vs. 25%), and with significantly greater reduction in symptoms of depression and anxiety.²⁴

In summary, these preliminary studies indicate the experience of the investigative team in conducting successful depression intervention research in India, in primary care practices enrolling older adults in northern Europe and the US, and in socioeconomically disadvantaged older adults in the US. The interventions have encompassed both prevention and treatment-focused goals, and they have spanned learning-based and skills-enhancing approaches such as psychoeducation and structured psychotherapies (IPT, PST, and BBTI) delivered in primary care and community agency settings by mental health nurses and by lay health counselors.

Research Approach: Experimental Design and Methods

The project time line is displayed in the figure below.

Introduction: We will follow the Medical Research Council guidelines for developing and evaluating complex interventions:²⁹ These guidelines seem particularly appropriate to the goals of the NIMH R34 program because they emphasize: (1) the importance of a sound theoretical understanding of how interventions cause change (or protect from depression, in the case of prevention); (2) that lack of effect may reflect implementation failure rather than genuine ineffectiveness, thus underscoring the need for a thorough evaluation process to identify implementation problems; and (3) the importance of adequate sample sizes to take account of variability in outcome, a range of outcomes to optimize use of data, and adaptation to local settings. We have adhered to MRC guidelines in the proposed formative and pilot phases of developing depression prevention interventions for use in LMIC, guided by the work of Patel and colleagues¹³ and Chatterjee and colleagues³⁰ in Goa.

We will conduct phases 1 and 2 in two public primary care centers: (1) Rural Health and Training Center, Mandur, Goa. The center is run by the Department of Preventive and Social Medicine, Goa Medical College. The center has a 20-bed primary care facility with 24-hour emergency facilities and a specialty mental health clinic and serves a population of 30,000; (2) Urban Health Center, St. Cruz, Goa. This is an urban health center also under the Department of Preventive and Social Medicine at Goa Medical College. It provides emergency and primary care to a population of 10,000. The Goa site PI, Amit Dias, M.D., has previously worked in these settings and has the necessary relationships in place to move forward. Additional information about the patient population is provided under Human Subjects.

Project Time Line

Phase 1 (Months 1-12): Formative Research

- develop draft MANAS/DP manual based on existing sources and evidence
- conduct intervention development workshops with professionals and civil society participants
- conduct pilot study of an uncontrolled case series (n=20) to inform final development of manual
- develop recruitment and assessment protocols for RCT
- develop a randomization procedure for RCT

Phase 2 (Months 13-36): Pilot Depression Prevention Randomized Clinical Trial (n=120)

- collect measures of feasibility, acceptability, tolerability, and safety
- analysis of measures and preparation of application for confirmatory depression prevention trial

Phase 1: The main task of phase 1 formative work (**months 1 – 12**) is to develop an intervention manual for MANAS/DP, that is, a MANAS-based depression and anxiety prevention manual with delivery strategies for use by Lay Health Counselors (LHCs) that will likely incorporate both MANAS psychoeducational/self-management interventions and other promising interventions indicated by our review of the global prevention literature (such as problem solving therapy of brief behavioral treatment for insomnia).

Phase 2 (pilot randomized prevention trial: **months 13-36**) will randomize 120 older adults to the adapted MANAS/DP or enhanced usual care in order to test feasibility and to provide pilot data to support a larger, adequately-powered trial. In keeping with the R34 program announcement, the objectives for the pilot prevention RCT address primarily feasibility, acceptability, tolerability and safety, by: (1) estimating recruitment and retention rates; (2) defining and testing the randomization procedure; (3) evaluating the reliable implementation of the MANAS/DP intervention; (4) assessment of measurement reliability (including strategies to minimize missingness rates and adequacy of measures to assess blindness of outcome evaluations); and (5) study management, data management/analysis.

Phase 1 (Months 1-12): Formative Research for the development of the MANAS Depression Prevention Intervention (MANAS/DP) Manual

The work of Phase 1, which will be guided by prior experience with formative work for the MANAS treatment (MANAS/RX) trial, will encompass: (1) synthesizing current global and local evidence on prevention of depression and associated anxiety disorders; (2) conducting intervention development workshops with two types of participants; and (3) training the LHCs and piloting the intervention's delivery in a non-randomized trial of 20 subjects in the same clinical settings as the phase 2 RCT. The primary deliverable of this Phase will be an intervention manual which details the components and delivery format for evaluation in Phase 2.

Procedure

1) Synthesis of the evidence

The goal of this method is to synthesize the global evidence on prevention of depression and anxiety disorders, including local evidence and evidence from other low-resource settings; and explanatory models related to the causal understanding and help-seeking in the local context. These issues are already being addressed through systematic reviews being carried out by the PREMIUM program, led by Patel, and are another example of how the proposed project will build on the ongoing work in Goa. PREMIUM (a Program for Effective Mental Health In Under-Resourced Health Systems) seeks to develop and evaluate culturally appropriate psychological treatments for depression and alcohol use disorders deliverable by LHCs. We will use the existing evidence to map out the specific components of depression and anxiety prevention identified in the global and local evidence; the process by which the component could lead to the desired outcome; the feasibility, acceptability, tolerability, and safety of the individual components; the potential risks of each component and how these could be reduced; the potential barriers to the implementation of each component and how these could be addressed; the minimum skills needed to deliver these components; and the gaps in the evidence base which need to be addressed through our proposed primary research in Phase 1.

2) Intervention Development Workshops

The goal of this method is to refine the composition of the intervention, elaborate its delivery format, and identify cultural, or stigma-related ethical barriers that might limit delivery or any part of the intervention.

We plan intervention development workshops with two types of participants, viz., health practitioners who work with elderly people at risk for depression, and with representatives of organizations of older people. Apart from offering a potent qualitative methodology for generating ideas on the composition and delivery of the intervention, these workshops also serve the purpose of engaging primary beneficiaries in research. The participants for the health professionals workshop will comprise of national and local experts in geriatric medicine and psychogeriatrics while the civil society workshop will comprise national and local representatives of civil society groups concerned with the welfare of older people, e.g., HelpAge India. We expect about 14-16 participants in each workshop. The Goa team has extensive experience of conducting such workshops as part of the PREMIUM program. The workshop begins with a presentation of an overview of the potential components of the MANAS/DP intervention identified in the global and local evidence (e.g., psychoeducation,

deep breathing, social casework, behavioral activation, Problem Solving Therapy, Brief Behavioral Treatment for Insomnia). A series of qualitative techniques, as elaborated in Table 1, will then be conducted to derive a model or framework for the intervention and to identify barriers that may occur during its delivery and strategies to address these.

Table 1: Intervention development workshop methodology:

Objective	Data collection method	Description	Method of analysis	Outputs
Organize the intervention strategies into a coherent framework and phases of delivery	Pile sorting and scheduling (Nominal group technique)	Participants are presented with index cards having the names of intervention strategies derived from the synthesis of the evidence. They then, in smaller groups of 7-8, sort out these cards into various piles of shared meaning and explain their reasoning. Participants then organize the piles of strategies into phases of temporal sequence and explain their reasoning.	Thematic analysis with substantiating quotes for qualitative data on explanations given for pile sorting/scheduling	An intervention framework that will be contrasted and compared with existing and subsequently derived frameworks at the second workshop
Elaborate the techniques used to deliver the intervention	Free listing	In small groups, participants discuss and free-list the techniques they can think of that relate to specific strategies. These are collated and discussed along with any other techniques derived from the literature.	Frequency graph or table of techniques followed by ranking according to their frequency	A list of techniques and their ranking
Define the competencies for LHCs to deliver the intervention; training and supervision requirements; risks, barriers & challenges in delivery; and how to address these.	Focus groups	A discussion in smaller groups of 7-8 participants.	Thematic analysis with substantiating quotes and summative content analysis	Themes related to the primary categories of analysis, e.g. core competencies, supervision requirements, etc.

A key output of this step will be a draft intervention manual which is used for piloting.

3) Piloting the MANAS/DP intervention

We propose to carry out a pilot study to determine and refine the operational elements of the intervention such as minimum number and duration of sessions, referral systems, and supervision structure and format (for example, group or individual supervision). Guided by previous work in preparation for MANAS/RX,²⁴ the pilot study will be conducted over four months in two primary health care centers and will involve patients attending those facilities. We will carry out a cohort study with 20 participants who meet our eligibility criteria to implement and evaluate the intervention. None of the facilities currently have counselors, and specialty mental health care is accessible only through referrals. We will recruit LHCs (women with the equivalent of a high school education, no prior mental health experience and having the attributes identified in our earlier work synthesizing the characteristics of effective lay mental health workers) who will be trained in the use of the

screening instrument chosen for the trial and to deliver the various components of the MANAS/DP intervention, based on a draft manual developed through our formative work. Training will be conducted conjointly by Drs. Chowdhary and Dias in Goa, and by experts at the Pittsburgh ACISR in PST and BBTI (Drs. Jennifer Morse and Anne Germain), using a group supervisory format via a web-based conference and training format such as Elluminate Live. At Pittsburgh, we have successfully used similar formats to train therapists at outlying sites.

We will collect two types of data for the assessment of this initial pilot phase: (1) process indicators; and (2) qualitative data. Proposed process indicators include the total number of patients in each facility aged 60 and older, the number excluded from undergoing screening on the basis of a priori exclusion criteria (less than 60 years old, inability to speak any of the local languages, in need of urgent medical care, already on an antidepressant medication or receiving mental health services, and refusal to answer), the number who screen positive for sub-threshold symptoms of depression or anxiety on the General Health Questionnaire (GHQ),^{31,32} the number/proportion of patients screening positive for sub-threshold (GHQ Score of 1-7 and who are non-cases on the revised Clinical Interview Schedule, see details below) symptoms who received the first psychoeducational session; the number/proportion of patients with ICD-10 common mental disorders who are referred out for treatment rather than prevention services, the number/proportion of patients with sub-threshold symptoms remaining in the MANAS/DP program who attend scheduled follow up appointments; and the number/proportion of patients who complete MANAS/DP and accept to participate in 12 month follow up interviews. Different components will be tested; the ordering and tailoring of components in a stepped-care format (with the highest step being referral out to a specialist care provider) will also be addressed during this phase. The LHCs will collect these data on a daily basis and collate them weekly for analysis.

Qualitative data will be derived from in-depth, semi-structured interviews with key informants (doctors, facility staff, health counselors, and patients) to document their perspectives about the feasibility, utility, and acceptability of various aspects of the intervention, as well as collecting information about the social and personal stressors (e.g., pain disability, isolation) that may put older persons at risk of depression and anxiety. The interviews with LHCs will, in addition, explore their perceptions of the training and supervision they received and the experiences, both positive and negative, of providing the interventions. The patient interviews will explore such issues as acceptability of the interventions, the preferred attributes of the LHCs, the desired outcomes of treatments, and the feasibility of the intervention, e.g., frequency, and duration of sessions. Apart from their overall opinion about the intervention, doctors and health facility staff will be asked about their perceptions of gaps in current treatments and how the MANAS/DP can effectively address these gaps.

Although MANAS/RX explored reasons for non-adherence, we expect that this issue will need to be re-examined when working specifically with older adults who are experiencing sub-threshold symptoms of depression and anxiety. We will use what we learn to implement strategies to improve retention and follow-up rates. Retention in our current depression prevention trial at Pittsburgh (Prevention of Depression in Older African Americans) and in MANAS/RX has been 80%. We will investigate reasons for adherence and non-adherence with MANAS/DP in order to frame an adherence management protocol in the initial assessment of and engagement with the patient, exploring possible risk factors for non-adherence and guiding the development of a careful plan to improve adherence at every step of the process of care delivery. In MANAS/RX we did this by interviewing subjects who had and had not adhered to the intervention. For MANAS/DP we will adapt the interview guide so that it focuses on why older adults might or might not follow the intervention regimen. We will also pilot the use of structured sentinel indicators (such as suicidal ideation) to enable supervision and monitoring of the program by the mental health specialist supervisors.

A key goal of the pilot study will be to test the adequacy of the GHQ (General Health Questionnaires) to define our target sample. Given the success of MANAS/RX in recruiting large numbers of participants, we anticipate being able to enroll patients with sub-threshold depression and anxiety (e.g., a likely range of GHQ scores of 1-7).

The thematic method of analysis of qualitative data will be used to generate results. Primary themes will reflect the research questions, for e.g. barriers to delivery and acceptability. Analysis will involve identifying, analyzing and reporting patterns in the interviews that reflect important issues relevant to the research themes. Codes will be inductively assigned to pieces of text. These coded pieces of text will be grouped together and then checked for emerging patterns. This will entail reading and re-reading interview transcripts, as well as

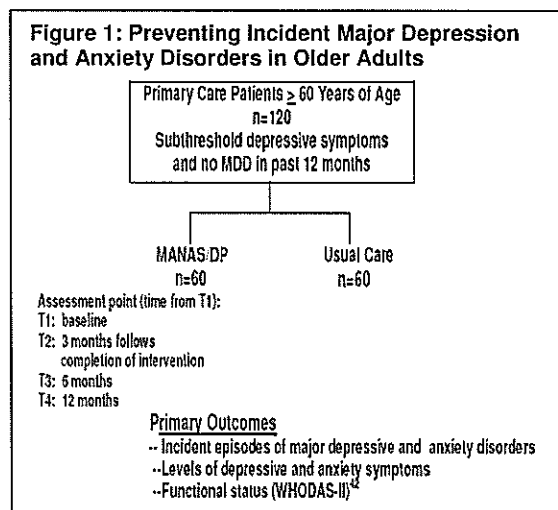
reviewing relevant literature and consultation with colleagues. Once all the interview transcripts are coded, segments of texts that are related to a common theme will be pieced together and in this manner emergent themes will be identified. The analysis will be performed using QSR International's NVivo 9 qualitative data analysis software.

A key output of this step will be a refined intervention manual, revised on the basis of the lessons of the pilot study, to be used in Phase 2.

Month 13-36: Phase 2 Pilot depression prevention randomized clinical trial (RCT) of MANAS/DP

Following the development and preliminary testing of the MANAS/DP manual in phase 1, we propose to randomize 120 older adults from the Rural and Urban Health Centers affiliated with Goa Medical College to the adapted MANAS/DP intervention or to enhanced usual care (EUC) in order to test feasibility and provide pilot data to support a larger, adequately-powered clinical trial. The feasibility objectives for the pilot RCT are to demonstrate successful : (1) recruitment, randomization, and retention; (2) reliable implementation of the intervention with demonstrated adherence to the MANAS/DP manual; (3) measurement reliability and adequacy of blinding procedures, and (4) collaborative data and study management.

Primary outcome: We will examine the cumulative incidence of episodes of major depression and anxiety disorders over a 12-month period in the two arms of the study: MANAS/DP and enhanced usual care (Figure 1). We are tracking both depression and anxiety episodes because of their frequent co-existence as common mental health disorders in primary care. Previous Goa³³ and Amsterdam²¹ trials have tracked the incidence of both common mental disorders, and we are doing so in ACISR-based prevention trials in Pittsburgh. In the Amsterdam trial, for example, incident anxiety disorder diagnoses included panic disorder, social phobia, generalized anxiety disorder, or a combination of these. We will also track functional status via the WHODAS-II.³⁴ The onset of an episode of major depression or anxiety disorder will result in exit from the trial and referral for clinical care.



Fundamental Principles and Strategies to be Followed in Intervention Development and Testing

How? Because of the spectrum of risk for depression and anxiety disorders, interventions need to allow for some degree of tailoring to meet the specific needs of the individual (and his/her caregiver). Thus, we subscribe to a structured but tailored approach to delivering interventions that are responsive to individual needs and preferences. We are proposing to investigate interventions that have already been shown to be efficacious in previous treatment studies of depression and anxiety disorders (e.g., the MANAS/RX trial). Our focus now is to address the value of such preventive strategies as older

adults face the most pervasive stressors and risk factors for depression and anxiety disorders in old age, e.g., disabilities related to medical and cognitive comorbidities, social isolation, caregiver burden, and poor sleep.^{9;16}

Interventions? Guided by MANAS/RX, we will focus phase 2 efforts on the investigation of brief, learning-based, skills-enhancing approaches amenable to intervention by LHCs, already shown to have efficacy in the treatment of common mental disorders, and conducive to protective factors such as self-efficacy and resilience to stress. In addition to interventions demonstrated efficacious and practicable in MANAS/RX (education about symptoms, breathing exercises for anxiety symptoms, scheduling pleasurable activities to counteract symptoms of depression, and providing information about social and welfare organizations) potential depression prevention strategies could include the use of Problem Solving Therapy,²⁸ Brief Behavioral Treatment for Insomnia,^{25;35} and Dyadic Intervention focused on both caregivers and care recipients.³⁶

Control conditions? We propose to test a range of preventive approaches against enhanced usual care provided by the two partnering primary care practices.

Enhanced usual care; Results of repeated assessments of mood and anxiety among participants randomly assigned to EUC will be made known to participants and their physicians on an ongoing basis. In addition, we

will share a copy of the MANAS/DP manual with physicians caring for participants randomly assigned to care as usual. In this sense, care as usual is enhanced by the forwarding of assessments to physicians and patients, to allow them to act as they deem appropriate. While enhancing care as usual in this fashion may make it more challenging to demonstrate meaningful differences between the intervention and control arms of MANAS/DP, we believe that it is ethically appropriate to share such information. By monitoring all participants, regardless of randomized assignment, we will be able to identify early on those with need for clinical care for emerging major depression, anxiety disorders, and/or dementia.³⁷ As in the PROSPECT study, we will document the content of EUC, i.e., the extent to which participants assigned to usual care receive either psychosocial or pharmacologic intervention for depression or anxiety.

Content of PST and of Brief Behavioral Treatment for Insomnia as Potential Depression Prevention Components of MANAS/DP

The goal of PST for primary care patients (PST-PC) is to teach people how to: solve here-and-now problems that contribute to depression or risk for depression; increase self-efficacy and resilience to stress; and learn a more structured approach to coping with problems. PST-PC is usually delivered in 6-8 individual sessions over 6-12 weeks by a primary care nurse or social worker. In the development of MANAS/DP, we will examine the feasibility and acceptability of PST-PC delivery by LHCs. The steps of the PST-PC intervention include: (1) select and define the problem; (2) establish realistic and achievable goals for problem resolution; (3) brainstorming to generate several alternative solutions; (4) implement decision making guidelines; (5) evaluate and choose solutions; (6) implement preferred solution; (7) evaluate outcome; and (8) provide booster sessions at months 6 and 12. The rationale for the use of PST-PC is that it reduces depressive and anxiety symptoms, which are key risk factors for the development of syndromal major depression or anxiety disorders.^{28,38}

The goal of Brief Behavioral Treatment of Insomnia (BBTI) is to teach people strategies for improving sleep quality and enhancing daytime well-being. BBTI can be delivered in a single 45-minute intervention session, followed two weeks later by a 30-minute booster session. In studies of BBTI, the intervention has been delivered by a primary care nurse or clinical social worker. In the development of MANAS/DP, we will explore the feasibility and acceptability of BBTI delivery by LHCs. The stages of BBTI encompass: (1) education about sleep (including behaviors that promote or interfere with sleep quality); (2) behavioral instructions: a) reduce time in bed to closely match number of hours slept, b) get up at the same time every day of the week, c) do not go to bed unless sleepy, d) don't stay in bed unless you are asleep; and (3) booster session: review educational material, assess treatment adherence, modify recommended sleep schedule to allow more time in bed.

Eligibility: The GHQ will be used as a first-stage screener to identify those individuals who fall below a cut-point. However, because misclassification can occur, we would then interview all these subjects with the CISR; those who are "non-cases" will be invited to the trial, while those who are "cases" are referred to usual care. Specifically, participants will be patients at the two participating primary care centers, aged 60 or older, with GHQ scores 1–7, (i.e., sub-threshold depressive and anxiety symptoms), Hindi MMSE scores of ≥ 24 (to exclude those with dementia), no major episodes of depression or anxiety disorder within the past 12 months as determined by CISR (Revised Clinical Interview Schedule)³⁹ (which generates ICD-10 diagnoses), and no current antidepressant pharmacotherapy. The GHQ and CISR have been used in Goa, thus avoiding the need to translate and validate a new instrument, and can be administered by trained lay interviewers. In the MANAS/RX trial the GHQ was used for screening purposes. As with any screening tool, false positives were identified based on the second stage diagnostic interviews with the CISR. For the proposed prevention work, a key question is how to identify "definite" versus "sub-threshold" cases of depression or anxiety disorders, and then apply a stepped-care program, such that the former (i.e. patients with subsyndromal depression or anxiety) are referred to the physician and the latter receive MANAS/DP. In addition, we will document psychosocial stressors including illness-related disabilities, bereavement, social isolation, and chronic pain, all of which we have found, frequently co-exist with substantial symptoms of depression.³⁹ This strategy will allow us to cover inclusion criteria for both indicated and selective prevention.

Important measurement domains: Our review of the depression prevention literature¹ suggested a core of shared measurement domains in keeping with the general logic model articulated here: (1) depression and

anxiety (both categorical diagnostic measures and dimensional measures of severity), (2) comorbid medical burden, (3) social and physical disability, (4) insomnia, (5) pain, (6) cognitive status, (7) social isolation/support, (8) caregiver burden, (9) self-efficacy, and (10) problem solving skills. The measurement domains listed here will be captured in the R34 work. In addition, we plan to explore the feasibility of collecting and analyzing biosignatures of risk for depression under the auspices of the Biosignatures Unit within the Pitt ACISR.

Collaborative Stepped-Care Intervention: MANAS/DP will be based on a stepped care approach, which emphasizes the efficient use of scarce resources. The collaborative approach involves four key team members: the health or research assistant (who provides screening), the lay health counselor (who provides MANAS/DP tools for self-management, PST-PC, and/or BBTI), the primary care physician, and a mental health specialist (as needed for supervision of persons who develop syndromal major depression or anxiety disorders). LHCs will act as case managers for patients who score positive for sub-threshold symptoms and will take overall responsibility for delivering the components of MANAS/DP, under the supervision of the primary care physician and mental health specialist. The stepped-care algorithm is depicted below:

	<u>Recipient</u>	<u>Timing</u>	<u>Intervention</u>	<u>Health Worker Contact</u>
Screening (Step 1)	Patients screened for common mental disorders and sub-threshold symptoms	At first consultation	Advice about results from screening; advice about seeing a LHC	PCP; LHC
Management of patients with sub-threshold symptoms (Step 2)	Patients with GHQ score of 1 – 7 and CIS-R negative for current episode of MDD or anxiety disorder	At first consultation or at follow-up	MANAS/DP Intervention	LHC; PCP
Monitoring Outcomes (Step 3)	Patients who remain symptomatic	Patients who do not improve despite MANAS/DP or who worsen	Offer patient watchful waiting or possibility of antidepressant medication	PCP
Referral (Step 4)	Patients who "convert" to major depression or anxiety disorder	patients whose symptoms and impairment lead to MDD	offer antidepressant medication	PCP + MH Specialist if suicidal

Timing of assessments: Assessments will be conducted at baseline (T1), post-intervention (T2), 6 months post-intervention (T3), and 12 months post-intervention (T4). The CISR will be administered at baseline (T1) and at each of T2-T4 assessments by blinded independent research assistants to document the cumulative incidence of major depression and anxiety disorders. The Hindi Mini-Mental Status will be administered at baseline and at 1 year to document incident cases of dementia. The GHQ will be administered every three months to document the trajectory of symptoms of depression, suicidal ideation, and anxiety. The WHODAS-II will also be administered every three months to document the trajectory of functional status.

We also plan to use mixed methods to evaluate the interventions, including a qualitative component with a subsample of participants (n = 20) and their relatives, the lay health counselors and doctors, to assess the experience and impact of the intervention. This approach will offer opportunities to monitor reasons for adherence and assess unanticipated effects.

Feasibility Objective 1 - recruitment, randomization, and retention: We will conduct the phase 2 pilot RCT in months 13-36. Recruitment will take 12 months (an average intake of about 10 participants monthly or 2-3 per week). The pilot RCT will include all components of a future hypothesis-testing RCT, including site-specific, permuted-block randomization at the individual participant level (not cluster randomization), blinded assessment procedures, and full implementation of intervention. A computer-generated randomization

sequence for each of the two participating clinics will be created at Goa (not in Pittsburgh, as previously proposed). We will evaluate the success of the blind by having the independent health assistant guess the subject's assignment as each subject completes the trial and exits. For this phase of MANAS/DP development, we will randomize at the individual subject level. If a subsequent confirmatory trial is funded, then cluster randomization (following MANAS/RX) will be used. Dr. Anderson, Professor of Biostatistics at Pittsburgh, will oversee the randomization and data analyses.

We will monitor retention throughout the randomized prevention trial, recording when and why each subject drops out. We will finish Phase II by month 30, with the final 6 months of the project being devoted to collection of any outstanding follow-up data, evaluating feasibility objectives, preparing articles, and submitting a grant proposal to support a larger randomized prevention trial.

(2) Implementation of the intervention: Phase 2 will have full implementation of both MANAS/DP and of enhanced usual care (EUC), just like a full scale RCT. The exact characteristics of these interventions will be determined in Phase 1. We will continue to monitor and evaluate the study interventions during Phase 2. To monitor fidelity and competence in the delivery of the intervention, a random sample of approximately 10% of audio-taped recordings from the early, middle, and final phases of the intervention will be reviewed and rated, using standards established during phase 1, by an independent research assistant in Goa working under the supervision of Drs. Dias, Chowdhary and Cohen. We will also monitor the adequacy of implementation in terms of number of sessions attended by each subject and timed length of sessions. Feedback will be provided to LHCs individually and in group formats, as in the Reynolds et al. current PREVENTION trial (P60 MD000207; P30 MH090333). The ACISR at Pittsburgh has established methods for monitoring fidelity and providing feedback to clinicians. We propose to follow a "train-the-trainer" approach, i.e., certified trainers in PST or BBTI at the Pittsburgh ACISR will train LHCs at Goa via Skype or a web-based conference and training format such as Elluminate Live teleconference, using group supervisory formats. The investigators have convened via SKYPE in the preparation of this application.

(3) Assessment reliability: we will continue to monitor and evaluate assessment procedures during Phase 2. Missing data rates will be monitored on a weekly basis. We will track participant adherence with assessments. In order to evaluate reliability of interviewer – administered measures. Approximately 10% of sessions will be videotaped and viewed by another rater. Rater training/consensus calls that review audio taped assessments will maintain reliability and prevent drift, consistent with our experience in multi-site studies (e.g., PROSPECT). If reliability falls as measured by ICC falls below less than 0.90 on rater administered measures of continuous variables, or kappa less than 0.75 for CISR diagnoses, we will add further training and re-evaluation.

Data Management: Data will be collected using PDAs at the two participating clinics in Goa and managed at Sangath by Smita Naik, who will customize databases for the study. Sangath has experience with the use of these devices in a population based survey of alcohol use and sexual risk behaviors, the MANAS trial, and an ongoing multi centre randomized controlled trial testing interventions for people with schizophrenia. The PDA's are easy to use in the field, relatively robust to withstand field conditions, and the data outputs are immediately available in SPSS format. The key steps for Data Management are: programming the outcome evaluation tools for use in handheld computers; piloting the use of the PDA's; establishing and testing the procedure for data transfer from field researchers to the data manager; producing monthly reports on the progress of field work; merging of data files; and developing security procedures for data management (back-up of data; security of access). Data will be exported to Stata 10.0 for analysis.

Data Analysis: Data analysis will be led by Professor Stewart Anderson at Pittsburgh, within the Research Design and Biostatistics Unit of the Pittsburgh Depression Prevention ACISR (P30 MH090333). We will examine data descriptively using cross-tabulations, histograms, and tests for normality (with corrective actions, data transformation, or nonparametric alternatives, as needed). An appropriate technique, such as imputation strategies based in random regression models, will handle missing data. We will consider time to onset of major depression or anxiety disorder as an outcome to be modeled via survival analysis. Qualitative data gathered in this phase will be analyzed using the methods described above, under the supervision of Drs. Alexander Cohen and Neerja Chowdhary. As a pilot study, the randomized prevention trial will examine feasibility; outcome data, while examined, will not be used for hypothesis testing. Descriptive analysis of feasibility data will follow the same structure as feasibility objectives described below.

Feasibility Objective 1—recruitment, randomization, and retention

1. Acceptable recruitment feasibility will be defined as meeting 100% of targeted randomization ($n = 120$), with 20% or less of eligible subjects refusing randomization. Other studies based in Goa including MANAS¹³ and HomeCare for Dementia Caregivers²⁶ have been able to achieve 80% + participation and completion rates in clinical trials.
2. Randomization (permuted block) will be deemed adequate if the randomization scheme produces equal numbers of participants randomized to each condition. Information about the condition assigned will be provided only to team members who need to know it (i.e., LHCs, investigators, and coordinators). Independent evaluators will remain blind to randomization assignments. Correctly guessing intervention assignment not significantly greater than chance (kappa statistic) will be accepted as evidence of interval validity.
3. Acceptable retention feasibility will be defined as 80% or more of randomized subjects completing the post-intervention assessment.

Objective 2—implementation of the MANAS/DP intervention

1. Acceptability: 80% or more of sessions will be attended by subjects
2. Training will be deemed adequate if the LHCs score above a predetermined passing grade on fidelity and competence measures defined in a codebook developed during the first year of formative work.

Objective 3—assessment reliability

We will apply criteria previously specified. For self-report measures, 10% or less of data will be missing. For interviewer administered measures, 10% of data will be missing or incomplete, and inter-rater reliability will be high (kappa of 0.75 or higher for mood and anxiety disorder diagnoses on the CISR).

Consistent with the NIMH R34 program announcement, we do not plan to estimate effect sizes based on the small feasibility RCT proposed here because such estimates are likely to be unreliable. In planning for a possible subsequent confirmatory RCT, we will draw upon published estimates of effect sizes including meta-analysis published by consultant Pim Cuijpers.

HUMAN SUBJECTS

We will seek approval of the trial by the Institutional Review Boards of the University of Pittsburgh, the London School of Hygiene and Tropical Medicine, and Sangath and the Indian Council of Medical Research.

1. Study Management: Ensuring the safety of all participants in clinical research remain safe requires adherence to reliable and valid case identification, strict oversight of interventions and outcomes in both arms of a clinical trial, and ongoing supervision of clinical assessments. Primary care patients at the two participating primary care clinics in Goa who screen positive for subthreshold symptoms of depression or anxiety on the GHQ will be invited to participate in either the formative open prevention trial of phase I or the pilot randomized prevention trial of phase II. After receiving the study intervention, participants will be followed for one year to determine the incidence of either major depression or anxiety disorders. The CIS-R, a structured diagnostic interview that generates ICD-10 diagnoses, will be used to confirm the presence of these disorders. Over the course of the research, participants will be at risk for worsening of depression, anxiety, suicidal ideation, and increased cognitive impairment. For this reason, the research team will meet weekly to discuss and monitor active participants in the study, to review eligibility data of potential participants, and refer those who are not eligible to appropriate treatment outside the study. The meeting will be attended by the Goa site PIs (Drs. Amit Dias and Neerja Chowdhary), project coordinators, and lay health counselors. Drs. Reynolds, Cohen, Patel and Cuijpers will participate via a web-based communications platform. The first half of the meeting will be dedicated to discussion of potential participants, during which the research assistants will present the findings from their evaluations (lay health counselors will not be present for this part of the meeting). The second half of the meeting will review participant progress and discuss any participants that may be at risk for becoming worse either affectively or cognitively (research assistants will not be present during the second half of the meeting). These weekly meetings will ensure that the research team will: 1) be consistent in its decisions concerning selection and retention of participants; and 2) continually review the safety of participants.

The study communication structure will include weekly web-based communications platforms and telephone conferences and, when possible, in-person meetings at international conferences. The investigators have convened via SKYPE in the preparation of this application. Regular updates of CONSORT charts will be reviewed to monitor study performance, minutes of meetings will be maintained, and the study's progress monitored in real time and reported to all the investigators. The investigators will convene web-based or telephone conferences, as well as email communication, in order to coordinate and implement specific tasks that arise during the study or which are assigned by the Data Safety Monitoring Board. The investigators at the University of Pittsburgh, LSHTM, and Sangath have extensive experience with multi-site clinical trials.

2. Selection: Our objective in phase I is to study a total of 20 people aged 60 or older; and in phase II, a total of 120 people aged 60 or older. Inclusion and exclusion information follow.

Inclusion criteria: 1) age 60 and older; 2) General Health Questionnaire score of 1-7, which is indicative of subthreshold depression or anxiety; 3) absence of current episodes of major depression and/or anxiety disorders as determined by administration of the CISR; 4) not currently taking antidepressant medication (see below); 5) consent to the study; 6) Konkani/English/Hindi speakers; and 7) expected to be resident in Goa for the subsequent 12 months.

Exclusion criteria: 1) presence of any axis 1 psychiatric disorder or substance abuse; 2) moderate/high suicide risk, i.e., intent or plan to attempt suicide in the near future; 3) history of psychiatric disorders other than non-psychotic unipolar major depression or anxiety disorder; 4) dementia; MMSE below 24 or ICD-10 diagnosis of dementia; 5) patients taking cognitive enhancing medication or using other psychotropic medications, including antidepressants; 6) acute or severe medical illness; and 7) inability to speak Konkani/Hindi/English.

3. Rationale for exclusion of patients taking antidepressants: Such patients may have a partially treated episode of major depression and, as such, are not appropriately included in a trial on depression prevention. Individuals ineligible for the study and those who decline to participate in the study will be referred for clinical evaluation and, when needed, treatment at their primary care clinic.

4. Participant characteristics and availability: Participants will be recruited from two primary care clinics; the MANAS research team has a previous association with similar clinics. The MANAS team has published its methods for recruiting and retaining adults in mental health research.^{1,25,55} The data tabulated below describe socio-demographic and clinical characteristics of 332 older adult participants in MANAS/RX public health clinics. The majority of the participants will be of Goan origin (35-40% Christian; 60-65% Hindu; and 1-2% Muslim.) Approximately half of the participants will be widowed, and two-thirds will have had less than 5 years of formal education. Almost half were characterized as mildly ill, with 20% not making CIS-R criteria for a current mental disorder. In the latter group (not meeting criteria for current mental disorder), 47% scored 6 or 7 on the GHQ.

Table 1: Sociodemographic details for public health clinic patients => 60 years
N=332 unless otherwise specified

SEX	n	%
Male	81	24
Female	251	76
MARITAL STATUS (N=304)		
Never married	6	2
Married	150	45
Widow/Widower	147	44
Separated/Divorced	1	>1
ETHNIC GRP (N=304)		
Goan	302	91
Migrant	2	1
RELIGION (N=304)		
Hindu	211	64
Christian	93	28
EMPLOYMENT (N=304)		
Employed full time	8	2
Employed part time/Seasonal	39	12
Unemployed/Homemaker	252	76
Retired	4	1
Any other	1	>1
ICD 10 DIAGNOSIS (based on CIS-R)		
Major depressive disorder	48	14
Anxiety disorder	58	17
Mixed anxiety depression	102	31
Depressive disorder w/ comorbid anxiety disorder	59	18
No disorder	65	20

5. Procedures aimed to improve adherence to research: To minimize missed data, participants will be contacted 2-4 days before appointments to confirm that they are prepared to meet. Home visits will also be allowed. Anyone endorsing suicidal ideation will be scheduled for a same-day appointment and will be seen by a study investigator, with a mental health specialist (psychiatrist or psychologist) available as needed. The onsite co-investigators, Neerja Chowdhary (a psychiatrist) and Amit Dias (a geriatrician) will see clinical cases and either manage them or refer them to the primary health centers of Goa Medical College. At the eligibility assessment, a member of the study team will explain to participants that this is an initial meeting to determine study eligibility and that this will be determined by the study team within a week.

6. Sources of research material will include interviews with participants and their caregivers.

7. Potential risks of the study include potential for elevated distress when discussing troubling issues in their lives. However, MANAS/DP may include interventions like problem solving therapy or brief behavioral treatment for insomnia, which we anticipate will diminish distress. The goal of the research is to determine if behavioral and learning based interventions like these may prevent or delay the onset of common mental disorders like depression and anxiety. If participants show evidence of major depression or of anxiety disorders, they will be referred out of the study for appropriate clinical care by their PCP with mental health specialist back-up as needed from Dr. Chowdhary.

Serious Adverse Events (including suicidal attempts and suicide risk) Serious Adverse Events (SAE) will be defined as any untoward

medical occurrence that results in death, requires hospitalization or causes significant or persistent incapacity/disability, or in the opinion of the investigators represents other potentially significant harm to research subjects. Based on our previous experiences with trials for depression in the region, we will monitor three types of serious adverse events – suicide attempts, hospitalization and death – and we will follow a pre-defined protocol approved by the DSMB which will include a clearly defined pathway for provision of appropriate medical care.

Lay Health Counselors will be trained to assess degree of suicidal risk and to follow a predefined algorithm for the management of suicidal risk. Thus, based on responses to a screening checklist that assesses the balance of risk and protective factors, as well as the frequency and type of suicidal thoughts, potential participants will be categorized according to the following criteria:

- Low risk: absent or few reports of passive suicidal ideas, mild severity of depression, no immediate risks and adequate protective factors.
- Moderate risk: Persistent suicidal ideas but no concrete plans, moderately severe depression, one or more risk factors and limited protective factors.
- High risk: Persistent suicidal ideas with definite plans, severe depression, multiple immediate risk including feelings of hopelessness and limited protective factors.

Potential participants with moderate or high risk factors will be referred for treatment and will not participate in MANAS/DP.

In summary, Lay Health Counselors will actively monitor participants for all adverse events, in both arms, via regular follow-up and, in addition, all adverse events experienced by participants in both arms, will be documented by the counselors and collated by one of the investigators who will, in turn, ensure adherence with the relevant protocol and report outcomes to the Data Safety and Monitoring Board.

8. Data Safety and Monitoring

Data Safety Monitoring Plan: Data on recruitment, retention, clinical progress, side effects, confidentiality, and safety for each subject will be reviewed at weekly conferences chaired by the Principal Investigator in Goa and attended by the local research team (including the project coordinator, lay health counselors, research assistants, and data management staff). Drs. Reynolds, Cohen, Cuijpers, and Patel (when he is not in Goa) will participate in these conferences via teleconference methods. These data will be incorporated into a longitudinal clinical report for each subject that permits a detailed weekly overview of each subject's participation and progress from the point of recruitment to the point of study exit. An important clinical, scientific, and ethical dimension of our data safety and monitoring plan is the benefit afforded by repeated assessments of early detection of major depression, anxiety disorders, dementia, suicidality or a change in physical condition warranting medical attention. This information will be forwarded promptly to the subjects' primary care physician and/or agency-based clinician with our recommendations for further evaluation and treatment.

Data Safety and Monitoring Board (DSMB): The MANAS/DP project leadership will assume responsibility for constituting an independent Data Safety Monitoring Board (DSMB) to oversee the trial. Membership of the DSMB will encompass expertise in psychiatry, primary care, biostatistics, and social science (e.g. medical anthropology). Data provided to the DSMB will include information on targeted and actual enrollment, data security and confidentiality, protocol conduct, benefits and adverse effects of protocol participation, and planned analyses.

9. Potential for Impact of MANAS/DP: This study will generate the first evidence of potentially scalable interventions for prevention of depression and anxiety in later life from a LMIC witnessing rapid demographic transition.

INCLUSION OF WOMEN AND MINORITIES

We project that two-thirds of study participants will be women. All participants will be native residents of Goa, India. There are no underrepresented minority subjects in the Goan population.

Program Director/Principal Investigator (Last, First, Middle):

Reynolds, Charles F. III

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Prevention of Depression and Associated Anxiety Disorders in Low and Middle Income Countries

Total Planned Enrollment: 120

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Females	Males	Total
Hispanic or Latino	0	0	0
Not Hispanic or Latino	80	40	120
Ethnic Category: Total of All Subjects *	80	40	120
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	80	40	**120
Racial Categories: Total of All Subjects *	80	40	120

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

**All subjects will be Konkani speakers residing in Goa, India.

Please see further characterization of subjects in the Human Subjects section.

INCLUSION OF CHILDREN

The focus of this work is prevention of depression in later life, thus children will not be eligible for this study.

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